IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Habib Zaghouani, et al.	Title:	Sustained Treatment of Type 1 Diabetes After Expression of Predisposition Markers
App. No.:	10/681,788	Art Unit:	1644
Conf. No.:	6701	Examiner:	Edwoldt, Gerald R.
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Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

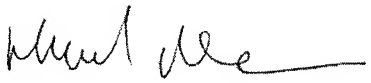
I, Habib Zaghouani, do hereby declare and say:

1. I am a citizen of the United States and my current residential address is 1608 Brookfield Manor, Columbia, Missouri, 65203.
2. I obtained my undergraduate degree in biochemistry from University of Paris, France in 1981. I obtained a Ph.D. in immunology from the University of Paris/Cancer Research Institute, France in 1987.
3. I am presently the J. Lavenia Edwards Chair in Pediatrics, Director, Center for Cellular and Molecular Immunology and Professor, Department of Molecular Microbiology & Immunology and Department of Child Health at the University of Missouri.
4. I have over one hundred publications and abstracts in the field of immunology. Please refer to the copy of my *curriculum vitae* in attached Appendix A for more details.
5. I am a named inventor on the '788 application as well as on related co-pending application serial numbers: 10/510,411; 11/290,070; and 11/425,084.
6. I have performed an experiment examining the impact of administration, initiated at the pre-diabetic stage, of soluble Ig-GAD2 to NOD mice over a period of 56 weeks. Data are provided in attached Appendix B.
7. NOD mice were assessed for blood glucose beginning at week 12 of age. Those mice that reached glucose levels of 160 – 250 mg/dl between week 14 to 25 received the following Ig-GAD2 regimen: 500 μg of soluble Ig-GAD2 i.p. daily for 5 days and then weekly injections thereafter for either 15 or 25 weeks. Blood glucose monitoring was performed during this period.
8. Overall, 100% of mice that became pre-diabetic at the age of 14 – 25 weeks and that were not treated with Ig-GAD2 progressed to diabetes (blood sugar level 300 mg/dl glucose) within 5 weeks after diagnosis of the pre-diabetic stage. Moreover, 60% of mice undergoing the 15-week treatment regimen were protected against diabetes throughout the

25 week post-hyperglycemia monitoring period. Interestingly, one mouse (Figure 1 B, left panel, open stars) progressed to diabetes by 5 weeks of treatment and 3 mice (Figure 1 B, plus, open diamond, and open pentagon) had similar disease manifestations shortly after interruption of the treatment.

9. When the regimen was extended to 25 weeks, 100% of the Ig-GAD2 treated animals were protected (Figure 1 A, right panel) and normoglycemia was restored in all mice (Figure 1 B, right panel). This status persisted throughout the duration of the study, which was terminated when the mice were 52 to 56 weeks of age.
10. Blood glucose levels for sol Ig-GAD2 (through week 24 of treatment) treated mice are shown in Table 1. Blood glucose levels for the untreated mice are shown in Table 2.
11. It is my professional opinion that the NOD mouse model is an appropriate and well accepted animal model for Type I diabetes.
12. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

December 19, 2007



Date

Habib Zaghouani, PhD

APPENDIX A

Curriculum Vitae Habib Zaghouani

EDUCATION

Ph.D.	1987	Immunology, University of Paris/Cancer Research Institute, Paris, France.
M.S.	1983	Immunology, University of Paris/Pasteur Institute, Paris, France.
B.S.	1981	Biochemistry, University of Paris, Paris, France.

POSITIONS AND RESEARCH EXPERIENCE

2006-present Director, Center for Cellular and Molecular Immunology, The University of Missouri School of Medicine, Columbia, MO

2006-present: J. Lavenia Edwards Chair in Pediatrics, the University of Missouri School of Medicine, Columbia, MO

2006-present: Professor, Department of Child Health, the University of Missouri School of Medicine, Columbia, MO.

2001-present: Professor, Department of Molecular Microbiology and Immunology, the University of Missouri School of Medicine, Columbia, MO.

2000-2001: Associate Professor, Department of Microbiology, the University of Tennessee, Knoxville, Tennessee.

1994-2000: Assistant Professor, Department of Microbiology, the University of Tennessee, Knoxville, Tennessee.

1990-1994: Research Assistant Professor, Department of Microbiology, Mount Sinai School of Medicine, New York.

1987-1989: Postdoctoral Fellow, Department of Microbiology, Mount Sinai School of Medicine, New York. Mentor: Dr. Constantin A. Bona.

1983-1987: Graduate Research Assistant, Ph.D. candidate, Immunology, University of Paris/Cancer Research Institute, Paris, France. Mentor: Dr. Marc Stanislawski.

1981-1983: Graduate Research Assistant, M.S. candidate, Immunology, Pasteur Institute, Paris, France. Director: Dr. Arthur Dony Strosberg.

RESEARCH GRANT SUPPORT

A. Principal Investigator

Active

1). 2RO1 NS 037406, National Institutes of Health, March 2004 - February 2009. Modulation of autoreactive T cells. PI: Habib Zaghouani.

2). 1RO1 DK 065748, National Institutes of Health, April 2005-March 2008. Immune tolerance against type I diabetes in mice. PI: Habib Zaghouani.

3). 2RO1 AI 48541, National Institutes of Health, May 2006- April 2011. Regulation of neonatal immunity. PI: Habib Zaghouani.

4). 1R21 AI 068746, National Institutes of Health. July 2007 – June 2009. Mimotopes against type I diabetes. PI: Habib Zaghouani.

Pending

1). 1RO1 NS057194-A2, National Institutes of Health, April 2008 - March 2013. Regulation of autoimmune encephalomylitis. PI: Habib Zaghouani.

2). 2RO1 DK 065748-01, National Institutes of Health, April 2008-March 2013. Immune tolerance against type I diabetes in mice. PI: Habib Zaghouani.

B. Co-investigator, Mentor, or Key Personnel

Active

T32 GM008396, National Institute of General Medical Sciences (NIGMS), July 1991-June 2012. Molecular Basis of Gene Expression and Signal Processing. PI: Mark Hannink (Zaghouani: Mentor).

T32 RR007004, National Institutes of Health, July 2005-June 2010, Postdoctoral Training in Comparative Medicine. PI: Craig Franklin (Zaghouani: Mentor).

T90 DK71510, National Institutes of Health, September 2004 – August 2009. Bench and Back: Clinical biodetectives training. PI: Mark Milanick (Zaghouani: Mentor).

R90 DK71510, National Institutes of Health, September 2004 – August 2009. Bench and Back: Clinical biodetectives training. PI: Mark Milanick (Zaghouani: Mentor).

KO8 AR048671, National Institutes of Health, June 2005-April 2008, Cytokine regulation of collagen-induced arthritis. PI: Robert Ortman (Zaghouani: Mentor).

1G20 RR021327, National Institutes of Health, September 2004-August 2009. Equipment for the MU Life Sciences Center. PI: Lon Dixon, (Zaghouani: Key personnel).

1 G20 RR019711, National Institutes of Health, September 2004-Agust 2009. Renovation of MU Medical School Vivarium. PI: Lon Dixon. (Zaghouani: Key personnel).

U19AT003264-01, National Institutes of Health, September 2005 – August 2009. TICIPS: HIV/AIDS, Secondary Infections and Immune Modulation. Center grant. PI: William Folk (Zaghouani: Faculty Member).

Research Foundation Grant, Arthritis Foundation, April 2006 – May 2008. Synoviolin is a target for arthritis. PI: Deyu Fang (Zaghouani: Mentor).

C. Previous Support (PI: Zaghouani, H)

1). R21 AI 062796, National Institutes of Health, July 2005-June 2007. Immune tolerance in the newborn mouse. Yearly direct cost $150,000. PI: Habib Zaghouani. No cost extension 11/30/2007

2). 1RO1 AI48541, National Institutes of Health, May 2001- April 2006. Regulation of neonatal immunity. Yearly direct cost: $175,000. PI: Habib Zaghouani.

3). Astral Inc, October 2001- September 2004. Development of Approaches to Combat Autoimmunity. PI: Habib Zaghouani.

4). RO1NS37406, National Institutes of Health, January 2000- December 2004. Modulation of autoreactive T cells. PI: Habib Zaghouani

5). RG2967B-3, National Multiple Sclerosis Society, October 2002 – March 31, 2004 Down-regulation of encephalitogenic T cells. PI: Habib Zaghouani.

6). RG2967A2/1, National Multiple Sclerosis Society, April 99 - March 2002. Down-regulation of encephalitogenic T cells. PI: Habib Zaghouani.

7). Astral Inc: March 95 - July 2001. A novel approach to delete encephalitogenic T cells. PI: Habib Zaghouani.

8). RG2778A1/1, National Multiple Sclerosis, April 96 - March 1999. A deletional strategy for encephalitogenic T cells. PI: Habib Zaghouani.

9). Astral Inc:, September 97- August 99. Generation of human Ig chimeras carrying wild type or antagonist forms of myelin peptides. PI: Habib Zaghouani.

10). 1R41AI47496, (STTR): National Institutes of Health, September 2000-August 2001. Treatment of EAE using a novel delivery system. . Co-PI: Habib Zaghouani.

TEACHING EXPERIENCE

2004:	Microbiology 205 (Medical Microbiology) 3 credit hours, 8 lecture contact hours, 170 student, Spring semester, University of Missouri School of Medicine, Columbia.
2002-present:	Microbiology 304 (Immunology) 3 credit hours, 14 lecture contact hours, 30 students, Fall semester, Molecular Microbiology and Immunology, University of Missouri School of Medicine, Columbia.
2002-present	Microbiology 407 (advanced Immunology) 4 credit hours, 9 lecture contact hours, 18 students, Spring semester, Molecular Microbiology and Immunology, University of Missouri School of Medicine, Columbia.
2001-present:	Bio 4952, Undergraduate research, 3 credit hours, 1-2 students, Fall and Winter semesters
2001-present:	Bio 4950, Undergraduate research, 3 credit hours, 2-3 Students, Fall and Winter semesters
2001-present:	Direct Immunology Journal Club, 1hour/week all year around, 40 student, postdocs and faculty members
1995-2001:	Microbiology 430 (Immunology), 3 credit hours, 45 lecture contact hours, 100-120 students, Fall semester, Microbiology, The University of Tennessee, Knoxville.
1995-2001:	Co-direct Microbiology 602 (Microbial Pathogenesis Journal Club), 1 credit hour, 15 lecture contact hours, 10-15 students, Fall semester, Microbiology, The University of Tennessee, Knoxville.
1995-2001:	Co-direct Microbiology 603 (Immunology Journal Club), 1 credit hours, 15 lecture contact hours, 10-15 students, Spring semester, Microbiology, The University of Tennessee, Knoxville.
1995-2001:	Microbiology 401 (Undergraduate Research), 3 credit hours, 1-2 students per semester, Microbiology, The University of Tennessee, Knoxville.

1998: Microbiology 630 (Topics in Immunology), 3 credit hours, 10 lecture contact hours, 20 students, Spring semester, (Seminar Series) Microbiology, The University of Tennessee, Knoxville.

1998-2001: Microbiology 493 (Independent Study in Immunology), 6 students, 10 lecture contact hours, spring, Microbiology, The University of Tennessee, Knoxville.

1992-1994: 600-level Immunology course, 3 credit hours, 6 lecture contact hours, 10 students, spring, Microbiology, Mount Sinai School of Medicine, New York.

HONORS AND AWARDS

2006. Speaker, Keystone Symposia on Tolerance Autoimmunity and Immune Regulation. March 21-26, 2006. Beaver Run Resort, Breckenridge, Colorado. Presentation title: Tregs for or against diabetes.

2004: Research Equipment Award for the purchase of an ELISPOT Analyzer, Office of Research, The University of Missouri,

2003: Keystone Symposia Scholarship ($1,000) for poster presentation by Hyun-Hee Lee, a graduate student in the laboratory, the meeting was held in Snowbird, UT

2003: Honorable citation for poster presentation by Randal Gregg, a graduate student in the laboratory. Life Science week, University of Missouri-Columbia.

2001: Science Alliance Research Excellence Award, Oak Ridge National Laboratories and The University of Tennessee, Knoxville.

2000: Science Alliance Research Excellence Award, Oak Ridge National Laboratories and The University of Tennessee, Knoxville.

2000: Exhibit, Performance, and Publication Expense Award, Faculty Senate Research Council and Office of research Administration, The University of Tennessee, Knoxville.

1999: Chancellor's nomination for Howard Hughes Medical Institute Assistant Investigator Appointment, The University of Tennessee, Knoxville.

1999: Biological Equipment Award, Office of Research Administration/Science Alliance/Genome Science and Technology/Division of Biology, The University of Tennessee, Knoxville.

1999: Science Alliance Research Excellence Award, Oak Ridge National Laboratories and The University of Tennessee, Knoxville.

1999: Exhibit, Performance, and Publication Expense Award, Faculty Senate Research Council and Office of research Administration, The University of Tennessee, Knoxville.

1998: Science Alliance Research Excellence Award, Oak Ridge National Laboratories and The University of Tennessee, Knoxville.

1998: Exhibit, Performance, and Publication Expense Award, Faculty Senate Research Council and Office of Research Administration, The University of Tennessee, Knoxville.

1997: Biological Equipment Award, Office of Research Administration/Science Alliance/ Division of Biology/ Department of Microbiology, The University of Tennessee, Knoxville.

1997: Exhibit, Performance, and Publication Expense Award, Faculty Senate Research Council and Office of Research Administration, The University of Tennessee, Knoxville.

1990: Research Excellence Award, Alliance Pharmaceutical Corporation. San Diego, CA.

1987-1988: Scientist Exchange Award (Postdoctoral Fellowship), French Cancer Society, Paris, France.

1984-1987: Graduate Student Scholarship, French Cancer Society, Paris, France.

PROFESSIONAL SERVICE

2007: Chair, Block symposium, regulation of immune cell development and function, American Association of Immunologis, Miami, FL.

2006-2010: Panel member, Hypersensitivity, Autoimmune and Immune-mediated Diseases (HAI) study section.

2006: Chair, Block symposium, treatment of autoimmune disease, American Association of Immunologis, Boston, MA.

2006: Review panel member, research proposals on Neurosciences, La Marato de TV3 Foundation, Catalan Agency For Health Technology Assessment And Research

2005: Chair, Block symposium, Cytokines and autoimmunity, American Association of Immunologis, Experimental Biology Meeting, San Diego, CA.

2004:	Panel member, NIAID Biodefence Workshop, Immunization and Vacination in Special Populations, Division of Allergy, Immunology and transplantation, NIH, Bethesda, MD
2004:	Chair, Block symposium, Tolerance and regulation of autoimmunity, American Association of Immunologis, Experimental Biology Meeting, Washington DC.
2004-present:	Adhoc Reviewer, TTT Study section, National Institutes of Health
2004-present:	Adhoc Reviewer, HAI Study section, National Institutes of Health
2003	Adhoc Reviewer, IMS Study Section, National Institutes of Health
2003	Adhoc Reviewer, ALY Study Section, National Institutes of Health
2003-present:	Member, Molecular Biology Program, University of Missouri-Columbia
2003-present:	Member, Genetics Area Program, University of Missouri-Columbia
2003-present:	Member, Veterinary Pathobiology Area Program, University of Missouri-Columbia
2003-present	Scientific Consultant, Division of endocrinology and Diabetes, Unversity of Missouri, Kansas City, MO
2002-2004:	Scientific Consultant, Alliance Pharmaceutical, San Diego, CA.
2001-present:	Member of The Graduate Student Recruitment Committee, Department of Molecular Microbiology and Immunology, The University of Missouri School of Medicine, Columbia.
2000-2001:	Adhoc Reviewer, BM-1 Study Section, National Institutes of Health
1992-2000:	Editorial board member: *Viral Immunology*
1989-present:	Reviewer: Immunology Journals
2000:	Guest Editor, International Review of Immunology
2000-2001:	Chair, Graduate Student Advisory Committee, Genome, Science, and Technology program, Oak Ridge National Laboratories and The University of Tennessee, Knoxville.
1995-2001:	Member of The Graduate Student Recruitment Committee, Department of Microbiology, The University of Tennessee, Knoxville.
1998:	Member of Faculty Search Committee, Department of Comparative Medicine, College of Veterinary Medicine, The University of Tennesee, Knoxville.

1999: Panel Member: NIH/NCI, Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) Grant program. Flexible system to advance innovative research for cancer drug discovery by small business panel.

PROFESSIONAL MEMBERSHIP

2006-present: Member of the Henry Kunkel Society
1998-present: Member of the Society for Neuroscience
1992-present: Member of the American Association for the Advancement of Science.
1992-present: Member of the American Association of Immunologists.

PUBLICATIONS

Manuscripts published in peer-review journals

59. Bot, A., D. Smith, B. Phillips, S. Bot, C. Bona, and H. Zaghouani. **(2006).** Immunologic control of tumors by *in vivo* FcgR-targeted antigen loading in conjunction with dsRNA-mediated immune modulation. *J. Immunol*. 176:1363-1374.

58. Caprio-Young, J., J. J. Bell, H-H. Lee, J. S. Ellis, D. M. Nast, G. Sayler, B. Min, and H. Zaghouani. **(2006).** Neonatally Primed Lymph Node but not Splenic T Cells Display a Gly- Gly Motif Within the T Cell Receptor Beta Chain Complementarity Determining Region 3 (CDR3) That Controls Affinity and Lymphoid Organ Retention. *J. Immunol.* 176:357-364.

57. Yu, P., R. K. Gregg, J. J. Bell, J. S. Ellis, R. Divekar, H-H Lee, R. Jain, H. Waldner, J. C. Hardaway, M. Collins, V. K. Kuchroo, and H. Zaghouani. **(2005)**. Specific T regulatory cells (Tregs) display broad suppressive functions against experimental allergic encephalomyelitis upon activation with cognate antigen. *J. Immunol.* 174:6772-6780.

56. Gregg, R. K., J. J. Bell, H-H. Lee, R. Jain, S. J. Schoenleber, R. Divekar, and H. Zaghouani **(2005).** IL-10 diminishes CTLA-4 expression on islet-resident T cells and sustains their activation rather than tolerance. *J. Immunol.* 174: 662-670.

55. Gregg, R. K., R. Jain, S. J. Schoenleber, R. Divekar, J. J. Bell, H-H. Lee, P. Yu, and H. Zaghouani. **(2004)**. A sudden decline in active membrane-bound TGFβ impairs both T regulatory cell function and protection against autoimmune diabetes . *J. Immunol.* 173:7308-7316.

54. Li, L, H-H. Lee, J. J. Bell, R. K. Gregg, J. S. Ellis, A. Gessner, and H. Zaghouani. **(2004)**. IL-4 Utilizes an Alternative Receptor to Drive Apoptosis of Th1 Cells and Skews Neonatal Immunity Towards Th2. *Immunity.* 20: 429-440.

53. Bell, J. J., B. Min, R. Gregg, H-H. Lee, and H. Zaghouani. **(2003).** Break of neonatal Th1 tolerance and exacerbation of experimental allergic encephalomyelitis by interference with B7 costimulation. *J. Immunol.* 171:1801-1808.

52. Legge, K. L., Gregg, R. K. Maldonado-Lopez, R., Li, L., Caprio, J. C., Moser, M., and Zaghouani, H. **(2002)**. On the role of dendritic cells in peripheral T cell tolerance and modulation of autoimmunity. *J. Exp. Med.* 196:217-227.

51 Pack, C. D., Cestra, A. E., Min, B., Legge, K. L., Li, L., Caprio, J. C., Bell, J. J., Gregg, R. K., and Zaghouani, H. **(2001).** Neonatal exposure to antigen primes the immune system to develop responses in various lymphoid organs and promotes bystander regulation of diverse T cell specificities. *J. Immunol.* 167:4187-4195

50. Li, L., Legge, K. L, Min, B., Bell, J. J, Gregg, R., Caprio, J. and Zaghouani, H. **(2001).** Neonatal immunity develops in a transgenic TCR transfer model and reveals a requirement for elevated cell input to achieve organ-specific responses. *J. Immunol.* 167:2585-2594

49. Min, B., Legge, K. L., Li, L., Caprio, J. C., Gregg, R. K., Bell, J. J., and Zaghouani, H. **(2001).** Defective expression of CD40L undermines both IL-12 production by antigen presenting cells and up-regulation of IL-2 receptor on splenic T cells and perpetuates INFγ-dependent T cell anergy. *J. Immunol.* 166:5594-5603

48. Day, R. B., Okada, M., Ito, Y., Tsukada, K., Zaghouani, H., Shibuya, N., and Stacey, G. **(2001).** Binding site of chitin oligosaccharides in the soybean plasma membrane. *Plant. Phys.* 126:1-12.

47. Legge, K. L., Min, B., Caprio, J. C., Li, L., Gregg, R. K., Bell, J. J., and Zaghouani, H. **(2000).** Coupling of peripheral tolerance to endogenous IL-10 promotes effective modulation of myelin-activated T cells and ameliorates experimental allergic encephalomyelitis. *J.Exp.Med.* 191:2039-51.

46. Anderson, A. C., Nicholson, L. B., Legge, K. L., Turchin, V., Zaghouani, H., and Kuchroo, V. K. **(2000).** High frequency of auto-reactive myelin proteolipid protein (PLP)-specific T cells in the periphery of naïve mice: mechanisms of selection of the self-reactive repertiore. *J. Exp. Med.* 191:761-770.

a)

45. Min, B., Legge, K. L., Caprio, J. C., Li, L., Gregg, R., and Zaghouani, H. **(2000).** Differential control of neonatal tolerance by antigen dose versus extended exposure and adjuvant. *Cell. Immunol.* 200 :45-55.

44. Legge, K. L., Min, B., Pack, C. D., Caprio, J. C., and Zaghouani, H. **(1999).** Differential

presentation of an altered peptide within fetal central and peripheral organs supports an avidity model for thymic T cell development and implies a peripheral re-adjustment for activation. *J. Immunol.* 162:5738-46.

43. Min, B., Legge, K. L., Pack, C. D. and Zaghouani, H. **(1998).** Neonatal exposure to a self peptide-Ig chimera circumvents the use of adjuvant and confers resistance to autoimmune disease by a novel mechanism involving IL-4 lymph node deviation and INFγ-mediated splenic anergy. *J. Exp. Med.* 188:2007-17.

42. Legge, K. L., Min, B., Cestra, A.E., Pack, C. D., and Zaghouani, H. **(1998).** T cell receptor agonist and antagonist exert in vivo cross-regulation when presented on immunoglobulins. J. Immunol. 161:106-11.

41. Legge, K. L., Min, B., Potter, N.T., and Zaghouani, H. **(1997).** Presentation of a T cell receptor antagonist peptide by immunoglobulins ablates activation of T cells by a synthetic peptide or protein requiring endocytic processing. *J. Exp. Med.* 185:1043-53.

40. Brumeanu, T-D, Dehazya, P., Wolf, I., Bot, A., Bona, C., and Zaghouani, H. **(1996).** Engineering of double antigenized Igs carrying B and T cell epitopes. Immunotechnology 2:85-95.

39. Brumeanu, T-D., Zaghouani, H., and Bona, C. **(1995**). Purification of antigenized immunoglobulins derivatized with monomethoxypolyethylene glycol. *J. Chromatogr.* 696:219-25.

38. Brumeanu, T-D., Zaghouani, H., Elahi, I., Daian, C. and Bona, C. **(1995**). Derivatization with monomethoxypolyethylene glycol of Igs expressing viral epitopes obviates adjuvant requirement. ***J. Immunol***. 154:3088-95.

37. Zaghouani, H., Anderson, S., Sperber, K. E., Daian, C., Kennedy, R. C., Mayer, L. and Bona, C. **(1995**). Induction of antibodies to the human immunodeficiency virus type 1 by immunization of baboons with immunoglobulin molecules carrying the principal neutralizing determinant of the envelope protein. Proc. Natl. Acad. Sci.USA. 92:631-35.

36. Bona, C., Brumeanu, T-D and Zaghouani, H. **(1994).** Immunogenicity of microbial peptides grafted in self immunoglobulin molecules. Cell. Mol. Biol. 40 (suppl):21-30.

35. Brumeanu, T-D., Swiggard, W. J., Steinman, R. M., Bona, C., and Zaghouani, H. **(1993)**. Efficient loading of identical peptide onto class II molecules by antigenized immunoglobulin and PR8 virus. J. Exp. Med. 178:1795-99.

34. Brumeanu, T-D., Kohanski, R., Bona, C., and Zaghouani, H. **(1993).** A sensitive method to detect defined peptide among those eluted from murine MHC class II molecules. J. Immunol. Meth. 160:65-71.

33. Kuzu, Y., Kuzu, H., Zaghouani. H., and Bona, C. **(1993)**. Priming of CTLs at various stages of ontogeny with transfectoma cells expressing a chimeric Ig heavy chain gene bearing an influenza virus nucleoprotein. *International. Immunol.* 5:1301-07.

32. Zaghouani, H., Kuzu, Y., Kuzu, H., Swigard, W., Steinman, R., and Bona, C. **(1993).** Contrasting efficacy of presentation by major histocompatibility complex class I and class II products when peptides are administered within a common protein carrier, self immunoglobulin. *Eur. J. Immunol.* 23:2746-50.

31. Penney, C. L., Ethier, D., Dionne, G., Nixon-George, A., Zaghouani, H., Michon, F., Jennings, H., and Bona, C. **(1993).** Further studies on the adjuvanticity of stearyl Tyrosine and ester analogues. Vaccine. 11:1129-1134.

30. Kuzu, H., Kuzu, Y., Zaghouani, H., and Bona, C. **(1993).** In-vivo priming effect during various stages of ontogeny of an influenza virus nucleoprotein derived peptide. Eur. J. Immunol. 23:1397-1400.

29. Zaghouani, H., Steinman, R., Nonacs, R.,. Shah, H., Gerhard, W. and Bona, C. **(1993)**. Efficient presentation of a viral T helper epitope expressed in the CDR3 region of a self immunoglobulin molecule. *Science*. 259:224-27.

28. Shengqiang, L., Polonis, V., Isobe, H., Zaghouani, H., Guinea, R., Moran, T., Bona, C., and Palese, P. **(1993).** Chimeric influenza virus induces neutralizing antibodies and cytotoxic T cells against human immunodeficiency virus type 1. *J. Virol.* 67:6659-66.

27. Hall, B., Zaghouani, H., Daian, C. and Bona, C. **(1992)**. A single amino acid mutation in CDR3 of the 3-14-9 light chain abolished expression of the IDA 10 defined idiotype and antigen binding. *J. Immunol.* 149:1605-12

26. Nixon, A., Zaghouani, H., Penney, C. L., Lacroix, M., Dionne, G., Anderson, S., Kennedy, R. C. and Bona, C. A. **(1992)**. Adjuvanticity of stearyl tyrosine on the antibody response to peptide 503-535 from HIV gp160. *Viral. Immunol*. 5:141-50

25. Zaghouani, H., Krystal, M., Kuzu, H., Moran, T., Shah, H., Kuzu, Y., Schulman, J. and Bona, C. **(1992)**. Cells expressing a heavy chain immunoglobulin gene carrying a viral T cell epitope are lysed by specific cytolytic T cells. ***J. Immunol.*** 148:3604-09.

24. Zaghouani, H., Goldstein, D., Shah, H., Anderson, S., Lacroix, M., Dionne, G., Kennedy, R. C. and Bona, C. **(1991)**. Induction of antibodies to the envelope protein of the human immunodeficiency virus by immunization with monoclonal anti-idiotypes. *Proc. Natl. Acad. Sci. USA.* 88:5645-49.

23. Kaushik, A., Mayer, R., Fidanza, V., *Zaghouani, H.*, Lim, A., Bona, C. and Dighiero, G. **(1990)**. LY-1 and V-gene expression among hybridomas secreting natural autoantibody. *J. Autoimmunity.* 3:687-700.

22. Mayer, R., Zaghouani, H., Usuba, O. and Bona, C. **(1990)**. The LY-1 gene expression in murine hybridomas producing autoantibodies. Autoimmunity. 6:293-305.

21. Bonilla, F. A., Zaghouani, H., Rubin, M. and Bona, C. **(1990)**. VK gene usage, idiotype expression, and antigen binding among clones expressing the VHX24 gene family derived from naive and anti-id immune Balb/c mice. *J. Immunol.* 146:616-22.

20. Fidanza, V., Mayer, R., Zaghouani, H., Diliberti, M. A., and Bona, C. **(1990)**. Autoantibodies, LY-1 and immunoglobulin V gene expression in hybridomas obtained from young and old NZB mice. *Arthritis & Rheumatism*. 33:711-23.

19. Zaghouani, H., Bonilla, F. A., Meek, K. & Bona, C. **(1989)**. Molecular basis for expression of the A48 regulatory idiotype on antibodies encoded by immunoglobulin variable region genes from various families. *Proc. Natl. Acad. Sci. USA*. 86:2341-45.

18. Zaghouani, H., Fidanza, V. and Bona, C. **(1989)**.The significance of idiotype-anti-idiotype interactions in the activation of self reactive clones. Clin. Exp. Rheumatology. 7/S-3:S19-25.

17. Pinter, A., Honnen, W. J., Tilley, S. A., Bona, C., Zaghouani, H., Zolla-Pazner, S. and Gorny, M. **(1989)**. Oligomeric structure of gp41, the transmembrane protein of human immunodeficiency virus type 1. *J. Virol.* 63:2674-79.

16. Zaghouani, H., Pene, J., Rousseau, V. and Stanislawski, M. **(1988)**. A new strain specific cross-reactive idiotype with possible regulatory function expressed on Balb/c anti-α(1-3) dextran antibodies. *J. Immunol.* 140:3844-50.

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APPENDIX B

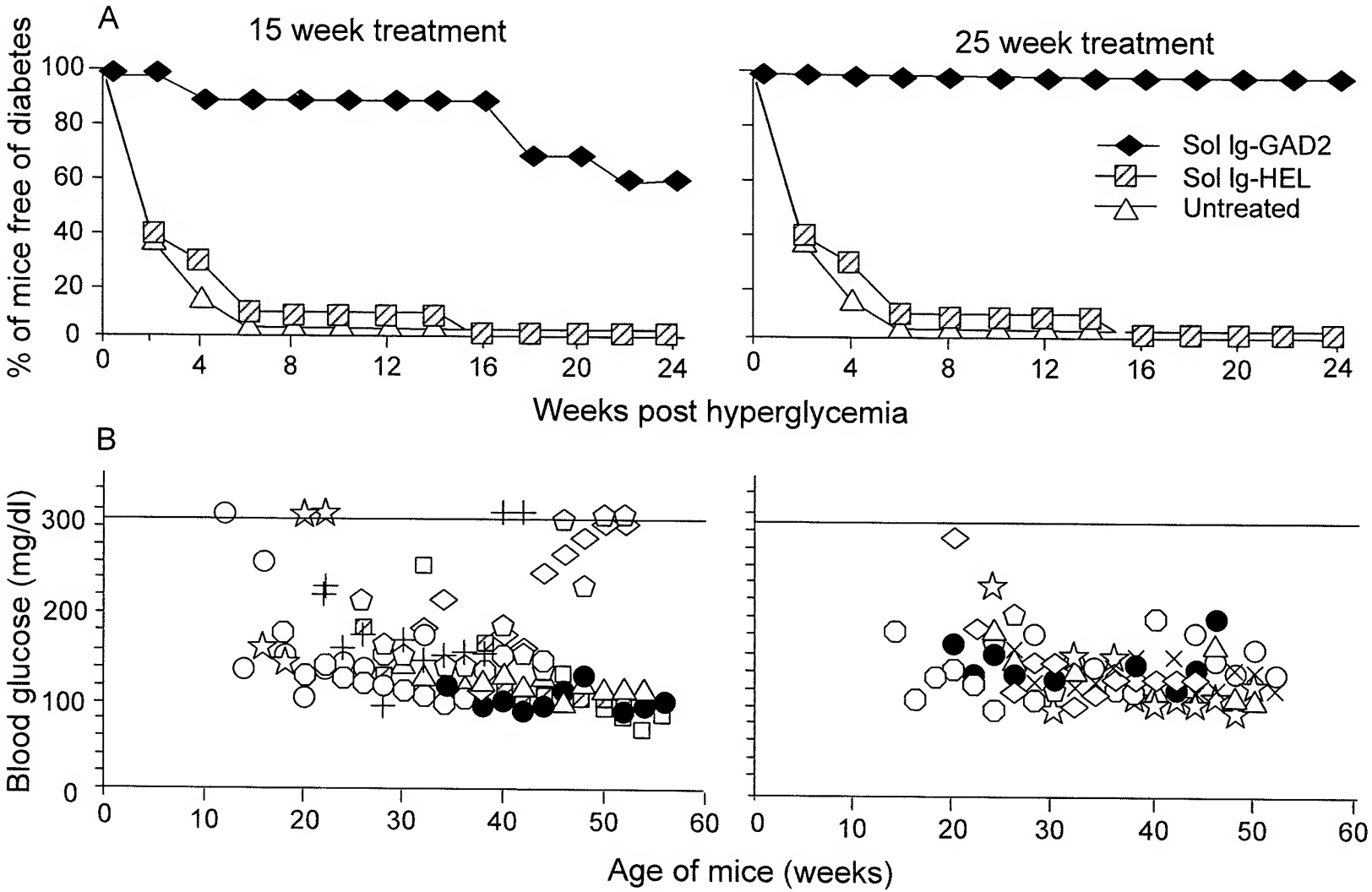
Table 1. Blood Glucose Levels (mg/dl) for Treated Mice

	Mouse													
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	161	165	180	182	165	250	179	212	160	229	232	224	180	173
1	252	125	134	159	144	137	129	179	152	258	183	154	165	199
2	176	119	213	127	144	136	169	165	146	162	227	192	152	148
3	121	117	145	121	117	255	142	228	281	285	217	186	112	111
4	149	110	127	148	126	179	124	151	390	176	214	156	159	132
5	131	144	175	117	116	153	126	128	351	98	99	161	140	136
6	148	132	114	136	150	126	123	143		94	134	97	118	156
7	98	99	146	133	93	105	121	156		89	120	179	135	134
8	128	111	178	152	113	158	119	139		170	127	172	134	108
9	109	104	140	110	120	138	153	147		147	134	142	116	132
10	118	108	160	138	120	140	121	141		145	170	132	117	151
11	151	91	192	144	101	145	113	152		143	112	114	135	163
12	107	91	244	161	130	151	109	216		150	124	149	121	97
13	107	101	256	124	113	137	108	184		142	114	130	148	137
14	85	81	264	125	116	112	119	155		154	127	154	118	143
15	133	113	198	96	120	118	99	156		147	119	178	123	158
16	136	91	285	112	128	103	112	127		153		144	146	157
17	111	129	377	105	111	148	107	134		228		123	123	111
18	127	99	366		98	158	113	148		350		159	122	93
19	99	110			111	176	137	338		339		170	132	
20	94	82			119	152	130	229				256	172	
21	83	96			114	135	153	331					215	
22	75	101				140	133	440						
23	70	99				140	154							
24	90	100				150	118							

Table 2. Blood Glucose Levels (mg/dl) for Untreated Mice

	Mouse						
Week	11	12	13	14	15	16	17
0	174	169	169	168	175	199	219
1	293	366	155	159	251	240	379
2	352	400	157	200	340	450	400
3	457	-	200	249	450	-	-
4	-	-	270	393	-	-	-
5	-	-	376	400	-	-	-
6	-	-	400	-	-	-	-

Figure 1


A
15 week treatment
25 week treatment
% of mice free of diabetes
100
80
60
40
20
0
0
4
8
12
16
20
24
Sol Ig-GAD2
Sol Ig-HEL
Untreated
Weeks post hyperglycemia
B
Blood glucose (mg/dl)
300
200
100
0
0
10
20
30
40
50
60
Age of mice (weeks)